STUDIES ON SERUM COPPER

II. The Copper Levels in Relation to Corticosteroid Administration*

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In the course of our assays of the copper level in blood sera of psoriatics, changes in the levels were noted which appeared to occur under the influence of systemic treatment with corticosteroid compounds (1). These changes have been subjected to further studies.

It is the purpose of this paper to report the pertinent observations made thus far—and to correlate the observations with a number of clinical and experimental findings obtained by previous investigators, which would conform with such an influence of corticosteroids.

METHODS AND SUBJECTS

The serum copper levels were assayed by means of the spectrophotometric method of Peterson and Bollier (1, 2). Analyses were performed shortly prior to the institution of steroid treatment, and were repeated thereafter at intervals of at least one week.

A total of 25 subjects participated in the study. These included 20 patients with psoriasis and 5 healthy volunteers. Of the 20 psoriatics, 15 were white males, 21 to 68 years of age, and 5 were white females, 13 to 38 years of age. Three of the 5 healthy volunteers were white males, 28 to 34 years old, while 2 healthy female volunteers were 42 and 49 years old.

All subjects received triamcinolone except one who was treated with methylprednisolone. Of the 20 psoriatics, 17 received triamcinolone orally, and 3 were treated with intralesional triamcinolone injections. Of the 5 persons without skin disease, 4 took triamcinolone, and the fifth methylprednisolone by mouth. The oral dosage of triamcinolone ranged from 8 to 32 mgm and that of methylprednisolone was 16 mg a day. The 3 patients injected intralesionally in this way received from 10 to 30 mg of triamcinolone acetonide once weekly for several weeks.

RESULTS

Some decline in the copper level was noted in most of the subjects during the period of approximately one to five weeks following initiation of the steroid treatment. On the basis of the data obtained it appears expedient to appraise this decline by comparing the levels found two weeks after start of the steroid treatment with those obtained prior to treatment†. Unfortunately, the assays were not repeated in all of the 25 subjects precisely two weeks after the start of treatment. It was necessary therefore to utilize the values found after one week in 4 individuals and the values found after three weeks for the remaining 2, as the basis for the comparison. In this way it was demonstrable that the serum copper level had declined from pretreatment values in 13 of 17 psoriatics who took steroids orally.

Four of the five non-psoriatic subjects on oral steroids and even all of the three psoriatic patients who received intralesional steroid injections showed some decline in serum copper. The drop in all of the 25 treated subjects averaged 0.54 mcg per ml.

This finding was in contrast to the relative individual constancy of the serum copper contents observed in 4 untreated healthy subjects and 3 untreated psoriatic subjects where a mean deviation from the first value by not more than 0.01 mcg/ml [in the direction of a decline] was noted in samples collected at random intervals of from one to four weeks. This stability of the serum copper levels per person has been substantiated also by previous assays (3).

The extent of the fall in serum copper levels observed after steroid administration did not appear to show any dependence on the steroid dosage employed, but considerable variations were noted in the response of different individuals to one and the same amount of steroid.

As examples typical of our results, the data obtained in 2 of the subjects are presented in Figures 1 and 2.

Whenever the serum copper level declined

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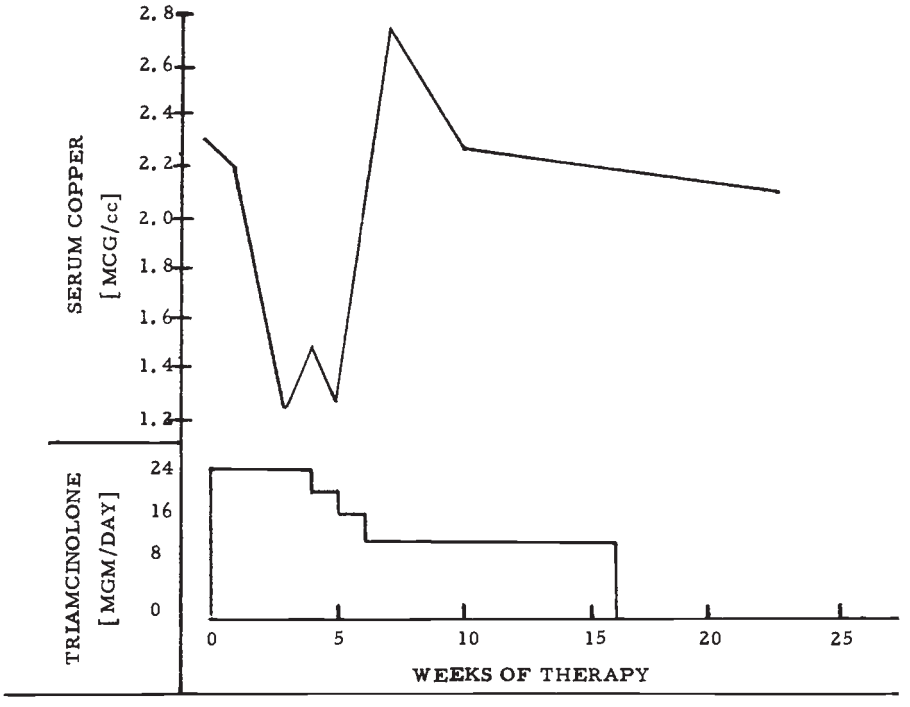

FIG. 1. Serum copper prior to and after oral triamcinolone administration

after institution of the steroid treatment, this change began within 1 to 2 weeks after the therapy was started, and usually reached its maximum in 1 to 3 weeks. At about that time, however, a "rebound" elevation of the copper level usually occurred to values higher than those obtained prior to treatment, until, after several months, stabilization was reached again at about the original level. The "swing" of the depressed copper values toward elevation—and then back to the original levels, occurred, regardless of whether the steroid medication was maintained, tapered off gradually, or stopped abruptly.

DISCUSSION

The trends observed appeared to be independent of the presence or absence of psoriasis, but were most likely related to the steroid administration. It is noted that a similar copper level curve was obtained after the use of methylprednisolone in 1 patient as was obtained in those receiving triamcinolone. However, additional controlled studies are required to confirm these impressions.

The fact that the wave-shaped "down-up-back" swing of the levels occurred in very similar

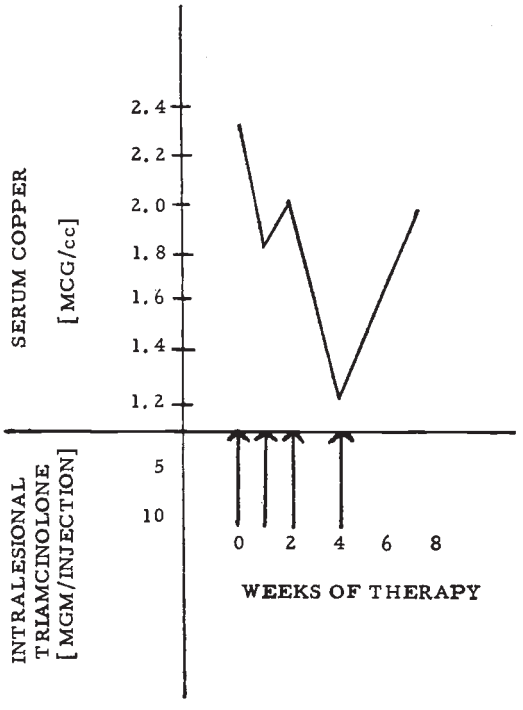

FIG. 2. Serum copper prior to and after intralesional injection of triamcinolone.

fashion, whether the steroid amounts were considerable or minor [intralesional injection], whether the administration was of long or short duration, etc., suggests a consistent occurrence of a depleting effect of any corticosteroid administration on the serum copper which is soon followed by some natural compensatory mechanism tending to restore the original level.

A number of previous clinical and experimental reports indicate the existence of an interrelationship between endocrine functions and blood copper levels; in particular, the adrenals, thyroid, pituitary and gonads appear to take part in this relationship.

In humans, serum copper levels were found to be elevated in hyperthyroidism (4–7), in Addison's disease (5, 6, 8), during the last trimester of pregnancy (5), and following administration of estrogens (9, 10). Low normal levels were observed in hypothyroidism (7). Decreased levels were observed in patients with acute leukemias treated with ACTH, regardless of the therapeutic response (5), and also in patients with rheumatic fever and rheumatoid arthritis treated with adrenocortical hormones (11).

El-Mofty *et al.* reported that in rats an increase in blood copper was produced by psoralens, provided that the pituitary gland was intact, and that this increase could be augmented further by adrenalectomy, and could be blocked or reversed by cortisone administration (12). Hundley and Ing by adrenalectomy succeeded in preventing completely the development of achromotrichia otherwise occurring in black rats under the influence of a copper deficient diet (13); once the achromotrichia had developed, the same authors partly or wholly reversed the change upon adrenalectomy or hypophysectomy (13).

In acute balance experiments, Wiesel found that single 30-minute I. V. infusions of 100 mg of hydrocortisone or 50 mg of prednisolone into normal humans produced a transient fall of serum copper, with the maximum decline at 2–3 hours; this was accompanied by a marked increase in urinary copper excretion (14). Evidence was also presented of the ability of glucogenic corticosteroids to chelate with copper *in vitro*, and it was proposed that such a mechanism could explain the effect of corticosteroids on the redistribution of copper in body tissues (14). In our own study, the corticosteroid was administered either orally or intracutaneously, never intravenously, and in considerably smaller amounts over a longer period of time; the decrease in serum copper levels did not become evident in most cases until after one week. If the serum copper decreases were due solely to a chelating effect of steroids, one should not expect to find a rebound elevation of copper during continued steroid administration.

From the evidence cited, it would appear that, in general, blood copper tends to vary in the same direction as thyroid function, but in an opposite direction to adrenal function. In this connection, it is interesting to note that thyroxine is capable of complexing very strongly with copper (15), so that increased circulating thyroid hormone might directly contribute to an elevation of blood copper.

It would also appear possible that the hypercupremia observed in association with various febrile conditions and with many subacute and chronic infections, might at least in part result from either reactively increased thyroid function and/or from some adrenocortical insufficiency caused by excessive stress.

SUMMARY AND CONCLUSION

1. Serum copper levels were determined weekly in 20 psoriatics and 5 non-psoriatics receiving adrenal corticosteroids orally or intralesionally. A tendency toward temporary lowering of serum copper was noted in 20 of 25 subjects.

2. The tendency toward lowering of serum copper appears to be a steroid effect, and not peculiar to psoriasis.

3. Previous clinical and experimental evidence was reviewed, which suggests the existence of an interrelationship between serum copper and several endocrine glands, especially adrenals, thyroid, and pituitary.

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